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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,801	12/10/2004	Stuart James Broughton	PG4860	8957
23347	7590	08/30/2005	EXAMINER	
GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY, MAI B475 FIVE MOORE DR., PO BOX 13398 RESEARCH TRIANGLE PARK, NC 27709-3398			GRAFFEO, MICHELLE	
			ART UNIT	PAPER NUMBER
			1614	

DATE MAILED: 08/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/517,801

Applicant(s)

BROUGHTON ET AL.

Examiner

Michelle Graffeo

Art Unit

1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 and 16 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 16 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. ____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>12/10/04</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Status of Action

The preliminary Amendment (Filed December 10, 2004) amended claims 2-10 canceled claims 11-15 and presented new claim 16. Claims 1-10 and 16 are pending and examined.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a condition for which an inhibitor of nitric oxide synthase is indicated, does not reasonably provide enablement for the prevention of all conditions for which an inhibitor of nitric oxide synthase is indicated. Claim 9 recites a method for the "prophylaxis" of a condition and "prophylaxis" is defined by Webster's New World™ Medical Dictionary as the prevention of a disease and therefore claims 9-10 are interpreted to include the prevention of a condition for which an inhibitor of nitric oxide synthase is indicated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) as to undue experimentation.

The factors include:

- 1) the nature of the invention;
- 2) the breadth of the claims;
- 3) the predictability or unpredictability of the art;
- 4) the amount of direction or guidance presented;
- 5) the presence or absence of working examples;
- 6) the quantity of experimentation necessary;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

- 1) the nature of the invention; the invention is directed to a method for the treatment of a condition for which an inhibitor of nitric oxide synthase is indicated.
- 2) the breadth of the claims; the scope of the method claims includes the prevention of all conditions for which an inhibitor of nitric oxide synthase is indicated.
- 3) the predictability or unpredictability of the art; the ability of preventing all conditions for which an inhibitor of nitric oxide synthase is indicated is not yet known in the art. The burden of enabling one skilled in the art to prevent all such conditions would be much greater than that of enabling the treatment of such conditions. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing said

conditions. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for preventing cancer.

Specifically, it is highly unlikely, and the Office would require experimental evidence to support the contention that the claim specified actives could actually prevent all conditions for which an inhibitor of nitric oxide synthase is indicated by simply administering, by any method, an amount of the claim specified active agents. The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for preventing such conditions.

The term "prevention" or "prophylaxis" is synonymous with the term "curing" and both circumscribe methods of treatment having absolute success. Since absolute success is not as of yet reasonably possible with most diseases/disorders, especially those having etiologies and pathophysiological manifestations which are as complex/poorly understood as the types of conditions indicated in the above claims, the specification is viewed as lacking an adequate enablement of where conditions for which an inhibitor of nitric oxide synthase is indicated may be actually prevented.

- 4) the amount of direction or guidance presented; the specification does not provide any guidance in terms of preventing conditions for which an inhibitor of nitric oxide synthase is indicated.
- 5) the presence or absence of working examples; no working examples are provided for preventing such conditions, for example in a patient, in the

specification. The applicant has not provided any competent evidence or disclosed any tests that are highly predictive for the preventative effects of the instant composition or method. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

6) the quantity of experimentation necessary; the quantity of experimentation would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of preventing such conditions, and the lack of working examples regarding the activity and method as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

In consideration of each of factors 1-6, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8,9,10 and 16 are rejected under 35 U.S.C. 102(b) as being anticipate by WO 93/13055 to The Wellcome Foundation Limited.

WO 93/13055 teaches a pharmaceutical composition (see page 1 lines 5-6) comprising (2S)-2-amino-4-{{2-(ethanimidoylamino)ethyl}thio} butanoic acid wherein R¹ is CH₃, Q is CH₂CH₂XCH₂CH₂ and X is S of the compound below (see Abstract):



a bulking agent, such as tragacanth (see page 10 line 12), which itself contains small amounts of cellulose and starch (claim 8), and an antioxidant (see page 9 line 30) for the treatment in a human (claims 9 and 16) of a condition where there is an advantage of inhibiting NO production from L-arginine by the action of NO synthase (see page 4 lines 15-20) such as arthritis (claim 10 – see page 5 lines 20-24).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/13055 to The Wellcome Foundation Limited in view of WO/98/30537 to Glaxo Group Limited and US Patent No. 6,297,281 to Chabrier de Lassaunier et al.

WO 93/13055 teaches a pharmaceutical composition (see page 1 lines 5-6) comprising (2S)-2-amino-4-[[2-(ethanimidoylamino)ethyl]thio] butanoic acid and a phosphoric acid thereof (claim 2 – see page 8 line 8) wherein R¹ is CH₃, Q is CH₂CH₂XCH₂CH₂ and X is S of the compound below (see Abstract):



a bulking agent, such as tragacanth (see page 10 line 12), which itself contains small amounts of cellulose and starch (claim 8), and an antioxidant (see page 9 line 30)

for the treatment in a human (claims 9 and 16) of a condition where there is an advantage of inhibiting NO production from L-arginine by the action of NO synthase (see page 4 lines 15-20) such as arthritis (claim 10 – see page 5 lines 20-24).

WO 93/13055 does not specifically teach solvates of (2S)-2-amino-4-[[2-(ethanimidoylamino)ethyl]thio] butanoic acid or any particular chelating agents and amounts thereof or amounts of bulking agents present in the pharmaceutical composition. Nonetheless, given the references below which describe chelating agents, one of ordinary skill in the art would through routine optimization appreciate the composition comprising 0.1 to 5% of the active agent, 80-99.5% of the bulking agent and 0.005 to 5% of the antioxidant particularly since bulking agents for example are used in higher amounts as a filler (claim 6). In other words, it would be obvious to one skilled in the art to use each additive in an amount appropriate for that additive.

The WO/98/30537 reference teaches the NO synthase inhibitor (2S)-2-amino-4-[[2-(ethanimidoylamino)ethyl]thio] butanoic acid and salts and solvates thereof (claims 2-5 – see page 2 line 26). Although the reference does not recite the particular solvates, mono and trihydrates, absent evidence to the contrary, one of ordinary skill in the art would appreciate the presence of such hydrates from the mention of solvates in the reference.

Chabrier de Lassaunier et al. teach a pharmaceutical composition containing at least one NO synthase inhibiting substance and at least one oxygen reactive form trapping substance (see Abstract) such as those substances with antioxidant properties (see col 2 lines 42-45) and in particular ascorbic acid (claim 7-see col 4 line 40).

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One of ordinary skill in the art would have been motivated to combine the above references and as combined would make obvious the invention as claimed. One of ordinary skill in the art would have been motivated to combine WO 98/30537 with WO 93/13055 because WO 98/30537 cites WO 93/13055. One of ordinary skill in the art would have been motivated to combine Chabrier de Lassaunier et al. with WO 98/30537 and WO 93/13055 because Chabrier de Lassaunier et al. teach the combination of at least one NO synthase inhibitor combined with another agent having antioxidant properties and both WO 98/30537 and WO 93/13055 teach NO synthase inhibitors and WO 93/13055 teaches the combination of a NO synthase inhibitor combined with an antioxidant as well. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

24 August 2005

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